CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
22-525

PHARMACOLOGY REVIEW(S)

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration

Division of Neurology Products (HFD-120)
Center for Drug Evaluation and Research

Date: June 15, 2010

From: Lois M. Freed, Ph.D.
Supervisory Pharmacologist

Subject: NDA 22-525 (Namenda XR Capsules; Forest Laboratories; August 21, 2009)

NDA 22-525 has been submitted by the sponsor (Forest Laboratories) to support marketing of an extended release formulation of memantine. The sponsor is the holder of NDA 21-487 (oral tablet for treatment of patients with Alzheimer's disease, approved 10/16/2003) and NDA 21-627 (oral solution for treatment of patients with Alzheimer's disease, approved 4/18/2005). The sponsor has also submitted INDs for memantine for other indications, including IND 73,075 for treatment of autism and IND (b) (4) for treatment of ADHD; IND 73,075 is currently active, whereas IND (b) (4) is inactive (as of 7/18/2007).

The sponsor provided no new nonclinical data to support NDA 22-525; however, the sponsor's proposed labeling includes a description of a juvenile animal toxicity study conducted in rats. Therefore, the dose-ranging and pivotal juvenile animal studies were reviewed for this application (Pharmacology/Toxicology NDA Review and Evaluation N22-525, David B. Hawver, Ph.D.). Based on his review, Dr. Hawver has recommended approval, but that the sponsor's description of the juvenile animal study results not be included in labeling. Dr. Hawver does recommend that the results of a 28-day oral combination neurotoxicity study of memantine and donepezil conducted in adult rats, reviewed previously (Pharmacology/Toxicology Review IND 33,392, David B. Hawver, Ph.D., 6/3/2010), be added to labeling.

I concur with Dr. Hawver's recommendations, including labeling recommendations as provided in his review, but have a few comments regarding the juvenile animal data and additional neurohistopathology evaluation in adult animals.

Juvenile animal study

In the pivotal study, memantine was administered at oral (gavage) doses of 0, 15, 30, or 45 mg/kg/day. For neurohistopathology assessment, animals (4/sex/group) were dosed

either once (on PND 14) and sacrificed on PND 15, or dosed on PNDs 14, 15, and 16 and sacrificed on PND 17. Neurodegeneration was detected in two brain areas, the anterior ventral nucleus of the thalamus (AVNT) and the lateral nucleus of the mammillary bodies (LNMB); the data (provided for individual animals) are summarized below (based on Dr. Hawver's review). Severity scores are as follows: 0 = no finding, 1 = barely detectable, 2 = light, 3 = moderate, 4 = heavy/dense.

BRAIN AREA	PND	DOSES (mg/kg)															
		0				15				30				45			
		1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
MALES																	
AVNT	15	1	0	0	0	1	0	0	0	1	0	0	0	1	2	3	3
LNMB		0	0	0	0	0	0	0	0	1	0	0	0	2	2	2	2
AVNT	17	1	0	0	0	2	0	0	0	1	0	0	0	1	2	2	3
LNMB		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
FEMALES																	
AVNT	15	1	0	0	0	1	2	2	0	2	0	0	0	1	1	2	0
LNMB		0	0	0	0	0	0	0	0	0	0	0	0	1	1	2	0
AVNT	17	0	0	0	0	2	0	0	0	2	0	0	0	2	3	3	0
LNMB		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

As Dr. Hawver notes, there is a clear drug-related effect at the HD in both brain areas in animals treated on PND 14, and in the thalamus in animals treated on PND 14-16. The reason for a lack of effect in the mammillary bodies in animals treated on PND 14-16 is unclear.

This study has also been reviewed under IND 73,075 (Forest Labs; autism) in the Division of Psychiatry Products (DPP). Based on that review (IND 73,075 Pharm/Tox Preliminary Safety Review, Ikram M. Elayan, Ph.D., 8/31/2009), DPP concluded that the NOAEL for the neurodegeneration was 15 mg/kg, primarily due to the neurodegeneration detected in mammillary bodies in one MD male (PND 15). While that is a reasonable conclusion, I agree with Dr. Hawver that it is difficult to ignore the increase in neurodegeneration in LD females in the thalamus (compared to controls), even though there is no similar increase in MD females. The difficulty in determining a clear NOAEL may be due do the small number of animals evaluated, as Dr. Hawver points out. However, this NDA is for an adult population only; therefore, further assessment of the neurotoxic potential of memantine in juvenile animals is not necessary.

Neurotoxic potential in adult animals: the concern regarding the potential for memantine-induced neurotoxicity when memantine is administered in combination with donepezil is discussed in Dr. Hawver's review. Briefly, Creeley *et al*. (Creeley CE *et al*. *Neurobiol Aging* 29(2):153-167, 2008) reported marked potentiation of neurotoxicity (i.e., lower effect dose of memantine and more widespread effects) when memantine was administered to rats in combination with donepezil (both drugs administered intraperitoneally). Based on these findings, the sponsor was asked (under IND 33,392) to conduct a 28-day combination neurotoxicity study of memantine and donepezil administered by the oral (clinical) route. While the results of the study were consistent with those of Creeley *et al*. (2008), the actual incidence and severity of the findings were

notably less. Therefore, there was concern that acute (possibly more severe) effects may have been missed. The sponsor was asked to address this concern by conducting an acute-dose neurotoxicity study of the combination (IND 33,392, Agency Advice/Information Request letter, 5/20/2010). I would recommend that this study be made a post-marketing requirement (PMR) for this application.

Recommendations: from a pharmacology/toxicology standpoint, there is no objection to the approval of this application; however, it is recommended that an acute-dose neurotoxicity study of the combination of memantine and donepezil (as previously communicated to the sponsor under IND 33,392) be made a PMR for the NDA. Justification and wording for the PMR have been provided in a separate document.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22525	ORIG-1	FOREST LABORATORIES INC	NAMENDA XR(MEMANTINE HCL)ER CAPSULES

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LOIS M FREED
06/15/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	22-525
Supporting document/s:	1
Applicant's letter date:	August 21, 2009
CDER stamp date:	August 21, 2009
Product:	Namenda® XR Capsules (memantine HCl extended release)
Indication:	Treatment of moderate to severe dementia of the Alzheimer's type
Applicant:	Forest Laboratories, Inc., Jersey City, NJ
Review Division:	Division of Neurology Products
Reviewer:	David B. Hawver, Ph.D.
Supervisor/Team Leader:	Lois M. Freed, Ph.D.
Division Director:	Russell Katz, M.D.
Project Manager:	Teresa A. Wheelous

Disclaimer

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1 Executive Summary

1.1 Recommendations

1.1.1 Approvability

This application is approvable.

1.1.2 Additional Nonclinical Recommendations

If memantine is to be developed for a pediatric indication, then consideration should be given to requiring a new study to clearly establish the NOEL for neurodegeneration in male and female rat pups. The new study should include an expanded histopathology of the brain, with a thorough analysis of the rostral to caudal extent of the thalamus and the mamillary bodies, with at least 20 pups/sex/group given single doses of memantine HCl on PND14 for neurohistopathology, and appropriate numbers of animals in satellite toxicokinetic groups.

In a letter of 20 MAY 2010, the Sponsor was asked to further characterize the neurotoxicity of the combination of memantine and donepezil by conducting a single dose oral neurotoxicity study in adult female rats with memantine in the presence and absence of donepezil at a maximum tolerated dose. This study should be conducted as a PMR/PMC.

1.1.3 Labeling

The package insert label should be revised to include an accurate description of exacerbation of the memantine-induced neurotoxicity observed in adult rats in the presence of memantine, and the associated safety margins with respect to the expected plasma exposures at the proposed maximum clinical dose The description of the toxicity study in juvenile rats should be deleted since this study did not include enough animals per group to allow a definitive assessment of the no-effect level for treatment-related neurodegeneration in the brain. See Appendix 1 for detailed recommendations.

1.2 Brief Discussion of Nonclinical Findings

No nonclinical studies were included in this submission. However, the Sponsor's proposed new package insert labeling, updated to PLR format, contains a description of an oral toxicity study with memantine in juvenile rats that is not present in the current label. Therefore, the preliminary and definitive juvenile

animal studies, which were submitted in support of IND 73,075 (Memantine HCl for Autism, Division of Psychiatry Products), have been reviewed here. Also, an oral neurotoxicity study in adult female rats with memantine and donepezil alone and in combination, submitted and reviewed under IND 33,392 (Memantine HCl for Alzheimer's Disease, Division of Neurology Products), has been summarized here so that the results can be described in the label.

In the preliminary juvenile toxicity study, administration of memantine HCl to rat pups via oral gavage once daily from post-natal day (PND) 14 to PND 35 was well tolerated at 15 and 30 mg/kg/day, but dosing at 60 and 120 mg/kg/day was stopped on Day 4 due to clinical signs (decreased activity, prostration, labored breathing, and/or piloerection) and/or excessive body weight loss (15-30%).

In the definitive juvenile toxicity study, administration of memantine HCl to rat pups via oral gavage once daily from PND 14 to PND 70 resulted in small and/or transient changes at 30 and/or 45 mg/kg/day (e.g., final body weight reduction of up to 12%, and reduced habituation to auditory startle at the end of dosing but not at 3 weeks postdose). Delayed preputial separation and vaginal opening were observed at these doses, but no adverse effects were observed on fertility or reproductive parameters. No neurodegeneration was observed in brain sections stained with amino cupric silver.

Treatment-related minimal to moderate neurodegeneration was observed in the ventral anterior nucleus of the thalamus and/or the lateral nucleus of the mammillary bodies in rat pups sacrificed 24 hours following treatment for 1-3 days (PND14-16) with memantine HCl at 15, 30, and 45 mg/kg/day. The NOEL for neurodegeneration was 15 mg/kg/day for males (based on minimal neurodegeneration observed in the mammillary bodies in 1/4 M at 30 mg/kg/day compared to 0/4 Control M on PND 15) and < 15 mg/kg/day for F (based on minimal to mild neurodegeneration observed in the ventral anterior thalamus in 4/8 F at the low dose of 15 mg/kg/day compared to minimal neurodegeneration in 1/8 Control F on PND 15 and 17).

In the 28-day combination neurotoxicity study in adult female rats, the incidence and severity of neurodegeneration induced by memantine was increased with coadministration of donepezil at 10 mg/kg/day, but not at 3 mg/kg/day. Memantine at 60 mg/kg/day induced mild neurodegeneration in the retrosplenial cortex in 1/9 rats without donepezil and in 1/10 rats given 3 mg/kg/day donepezil; 60 mg/kg/day memantine combined with 10 mg/kg/day donepezil, however, induced neurodegeneration in 2/7 rats (moderate to marked lesions in several brain areas in one [e.g., temporal, perirhinal, entorhinal, insular, piriform, and frontal cortex], and mild lesions in the entorhinal cortex in the other). Marked neurodegeneration in the entorhinal cortex was observed in 1/9 rats at 30 mg/kg/day memantine + 10 mg/kg/day donepezil. The no-effect level of 10 mg/kg/day memantine + 10 mg/kg/day donepezil was associated with memantine plasma exposures approximately equivalent to (based on AUC), or two times

greater than (based on Cmax), those expected in humans given the MRHD of 28 mg/day Namenda® XR; and with donepezil plasma exposures approximately 3 times (based on AUC), or 6 times (based on Cmax), greater than those expected in humans given the MRHD of 10 mg/day donepezil.

2 Drug Information

2.1 Drug

2.1.1 CAS Registry Number

4110-52-1

2.1.2 Generic Name

Memantine Hydrochloride extended release capsules; 7, 14, 21, and 28 mg

2.1.3 Code Name

MRZ 2/145, SUN Y7017

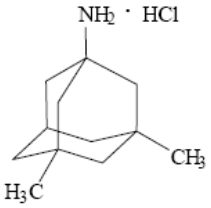
2.1.4 Chemical Name

3,5-dimethyl-1-adamantanamine hydrochloride,
1-amino-3,5-dimethyladamantane hydrochloride, and
3,5-dimethyltricyclo [3.3.1.13,7-] decan-1-amine hydrochloride

2.1.5 Molecular Formula/Molecular Weight

Molecular formula/molecular weight: $C_{12}H_{21}N \cdot HCl$ / 215.77

2.1.6 Structure



2.1.7 Pharmacologic class

N-methyl-D-aspartate (NMDA) receptor antagonist

2.2 Relevant IND/s, NDA/s, and DMF/s

NDA 21-487 Memantine HCl tablets for moderate to severe dementia of the Alzheimer's type, approved 16 OCT 2003, Forest Laboratories Inc.

NDA 21-627 Memantine HCl solution for moderate to severe dementia of the Alzheimer's type, approved 18 APR 2005, Forest Laboratories Inc.

IND 33,392 Memantine HCl tablets for moderate to severe dementia of the Alzheimer's type (originally for spasticity), Forest Laboratories Inc.

IND 73,075 Memantine HCl capsules for autism, Forest Laboratories Inc.

(b) (4)

2.3 Clinical Formulation

2.3.1 Drug Formulation

Memantine HCl is formulated with inactive ingredients (sugar spheres (b) (4)], povidone K30, talc, (b) (4)® (b) (4)® (b) (4) into beads, which are encapsulated into empty gelatin capsules. Each oral capsule will contain 7, 14, 21, or 28 mg memantine HCl.

2.3.2 Comments on Novel Excipients

There are no novel excipients in the clinical formulation.

2.3.3 Comments on Impurities/Degradants of Concern

No concerns.

2.4 Proposed Clinical Population and Dosing Regimen

Namenda® XR is indicated for the treatment of patients with moderate to severe dementia of the Alzheimer's type. The recommended therapeutic dosage is 28 mg once daily. Dosing should be initiated at 7 mg/day and titrated upward weekly in 7 mg increments, as tolerated, up to the maximum recommended dose of 28 mg/day.

2.5 Regulatory Background

This is an original NDA submission for an extended release oral capsule formulation of memantine hydrochloride for the treatment of moderate to severe dementia of the Alzheimer's type. Immediate release formulations were approved in 2003 (tablet) and in 2005 (oral solution).

3 Studies Submitted

3.1 Studies Reviewed

Memantine: Preliminary Toxicity Study in the Juvenile Rat
((b) (4) Study No. 04-2860; Forest Study No. MEMTX22000; submitted to IND 73,075)

Memantine: Toxicity Study in the Juvenile Rat
((b) (4) Study No. 04-2874; Forest Study No. MEMTX23000; submitted to IND 73,075)

3.2 Studies Not Reviewed

None.

3.3 Previous Reviews Referenced

IND 73,075 #000 Memantine for Autism, Pharm/Tox Preliminary Safety Review by Dr. Ikram Elayan

IND 33,392 #612 Memantine for Alzheimer's Disease, Pharmacology/Toxicology Review by Dr. David Hawver

9 Reproductive and Developmental Toxicology

9.2 Juvenile Animal Toxicity Studies

Memantine: Preliminary Toxicity Study in the Juvenile Rat
(Final Report; (b) (4) Study No. 04-2860; Forest Study No. MEMTX22000)

This study was conducted at (b) (4) Dosing was initiated on 21 or 22 OCT 2004 and terminated on 11 or 12 NOV 2004. Sprague-Dawley rat pups were dosed via oral gavage at 5 mL/kg in distilled water once daily from PND 14 to PND 35 with vehicle (10/sex) or memantine HCl (Lot # M00026, 101% purity) at 15, 30, 60, or 120 mg/kg/day (15/sex/gr). Satellite TK groups were sampled at PND 14 (10/sex Con, 1 & 8 hr postdose; 30/sex/gr drug, 5/sex/timepoint at 0.5, 1, 4, 8, 12, & 24 hrs postdose) and at PND 35 (10/sex Con, 1 & 8 hrs postdose; 15/sex/gr drug, 5/sex/timepoint, each animal was bled twice, at 0.5, 1, 4, 8, 12, & 24 hrs postdose). Evaluations included mortality, clinical signs, body weight, food consumption, and necropsy.

All animals at 120 mg/kg/day were euthanized by the Day 4 of dosing (PND 17) due to poor condition and sustained weight loss (~-30%). Prostration and labored breathing were observed in 1/15 M and 2/15 F after the first dose, piloerection was noted in 5/15 M and 6/15 F after the second dose, and all pups at this dose showed decreased activity on Days 2-4 of dosing.

Dosing at 60 mg/kg/day was discontinued on Day 4 (PND 17) due to decreased activity (Days 3-4, F only) and sustained weight loss (~-15%, Days 1-3, M & F).

No treatment-related effects were observed at 30 or 15 mg/kg/day. No treatment-related changes were observed in food consumption or necropsy in any dose group.

In this pilot oral toxicity study with memantine HCl in juvenile rats the NOAEL was 30 mg/kg/day; 60 mg/kg/day exceeded the MTD.

The table below shows the toxicokinetic data obtained after dosing on Days PND 14 and PND 35:

Table 3- Toxicokinetic Parameters of Memantine (Free Base) on Postnatal Days 14 (1 Day after Dose Initiation) and 35 (22 Days after Dose Initiation) following Oral Administration of 15, 30, 60 and 120 mg/kg/day of Memantine in Male and Female Juvenile Rats

Gender	Day	Dose (mg/kg/day)	T_{max} (hr)	C_{max} (ng/mL)	$AUC_{0.5-24}$ (hr*ng/mL)
M	14	15	1.0	1417.75	17775
M	14	30	8.0	2448.84	35595
M	14	60	1.0	4151.36	74186
M	14	120	1.0	8033.51	129172
M	35	15	1.0	1015.35	6249
M	35	30	4.0	1614.07	13059
F	14	15	1.0	1428.21	17539
F	14	30	1.0	2833.74	37503
F	14	60	1.0	4813.96	81806
F	14	120	1.0	11618.54	142925
F	35	15	1.0	1251.62	8689
F	35	30	1.0	1987.01	17865

(IND 73,075 Volume 4.2, page 106)

Memantine: Toxicity Study in the Juvenile Rat
(Final Report, submitted May 18, 2010 to IND 73,075 in Serial Number 114; (b) (4) Study No. 04-2874; Forest Study No. MEMTX23000)

Testing Facility: (b) (4)
Dosing Initiation: 04 MAY 2005
End of In-Life Phase: 20 SEP 2005
Report Date: 25 JAN 2007
GLP: US FDA GLP compliant, except for homogeneity, stability, and concentration verification of positive control.
QA: QA statement present, signed 25 JAN 2007
Study Completion: 25 JAN 2007

Drug: Memantine HCl
Supplier: Forest Labs, Commack, NY
Lot #: L0000567
Purity: 100%
Vehicle: Distilled water
Route: Oral gavage, 5 mL/kg

Positive Con: MK-801, i.p. (in 0.9% Sodium Chloride Injection, USP; 5 mL/kg)
Supplier: Forest Labs, Commack, NY
Lot #: 08K4610

Animals: Sprague-Dawley rats, Crl:CD® IGS BR, (b) (4) 61 dams with pre-culled litters (5 pups/sex) for memantine and control groups. 9 M and 9 F 8 wks old for positive control groups.
Age: PND 14 was the first day of dosing. (pups ranged from 27-44 g)
Positive control rats: 10 wks old at dosing (M 324-364 g, F 210-245 g).

Experimental Design:

Neurohistopathology:

- 4 pups/sex/group were euthanized on PND 15 after a single oral dose of 0, 15, 30, or 45 mg/kg memantine HCl on PND 14. Brains were perfusion-fixed for neurohistopathological evaluation.
- 4 pups/sex/group were euthanized on PND 17 after once daily oral dosing at 0, 15, 30, or 45 mg/kg/day memantine HCl on PND 14, 15, and 16. Brains were perfusion-fixed for neurohistopathological evaluation.

Main Study:

32 pups/sex/group given 0, 15, 30, or 45 mg/kg/day oral memantine HCl once daily on PND 14-70. Assessments included survival, clinical signs, body weight, and attainment of puberty.

- PND 70 subgroup:
  - 10 pups/sex/group were bled for clinical chemistry and hematology on PND 71 and then utilized for organ weights and standard histopathological evaluation.
  - 6/sex/group were perfusion-fixed for neurohistopathological evaluation.
- Post-treatment subgroup: 16 pups/sex/group were evaluated at PND 65-68 in the Auditory Startle Habituation Test (ASHT) and at least one week after the last dose in the ASHT and in three other neurobehavioral tests.
  - 10 pups/sex/group were evaluated in a mating trial at least one week after the last dose. Females were necropsied at GD 14; males were necropsied at approximately the same time; tissues were prepared for standard histopathological evaluation.
  - 6 pups/sex/group were sacrificed at approximately the same time as the mated cohort, but were perfusion-fixed for neurohistopathological evaluation. (Note: the perfusion fixative was prepared incorrectly for the sacrifice on 15 SEP 2005 and used for males 1043, 1044, 2043, 3043, and 4042; the remaining animals scheduled for perfusion on that date were perfused instead on 16 SEP 2005, using the correct perfusion fixative.)

Positive Controls:

- Eight adult (10-wk old) male rats were given a single dose of 10 mg/kg MK-801 i.p. (5 mL/kg) and were killed and perfusion-fixed for neurohistopathological evaluation at ~24 hrs postdose (N=4) or at ~72 hrs postdose (N=3, due to early death in one).
- Eight adult (10-wk old) female rats were given a single dose of 5 mg/kg MK-801 i.p. (5 mL/kg). Four of these were euthanized early for humane reasons because they became prostrate and did not show signs of recovery at 24 hrs postdose. Three of the remaining four females were killed and perfusion-fixed for neurohistopathological evaluation at ~24 hrs postdose. The fate of the fourth remaining female was not described in the report.

Toxicokinetics:

- PND 14:
  - 4 pups/sex/time point from each drug-treated group were terminally bled at 0.5, 1, 4, 8, 12, and 24 postdose.
  - 4 pups/sex/time point from the vehicle control group were terminally bled at 1 and 8 hrs postdose.
- PND 67:
  - 9 pups/sex/group from the 10/sex/group Main Study PND 70 animals not selected for perfusion-fixation were bled (via the retro-orbital plexus) to provide 3 samples/sex/time point (each animal was bled twice) at 0.5, 1, 4, 8, 12, and 24 postdose.
  - 6 pups/sex from the 10/sex/group Main Study PND 70 vehicle control group animals not selected for perfusion-fixation were bled (via the retro-

orbital plexus) to provide 3 samples/sex/time point (each animal was bled twice) at 1 and 8 hrs postdose.

Clinical Signs: (twice daily for overt toxicity; weekly detailed exam)

No treatment-related clinical signs were observed. Deaths of uncertain cause were observed in the following main study animals: 1/32 MDF (D21), 1/32 HDF (D4), and 1/32 HDM (D28). 1/32 Con F was euthanized due to an ulcerated mass (D111).

Body Weight: (PND 12, 14, 15, 17, 21, 25, 28, then weekly)

Final body weight on PND 70 was reduced 10-12% in HDM and HDF and 3-6% in MDM and MDF, compared to controls.

Food Consumption: (gravimetrically; PND 21 onward, coinciding with BW schedule)

Food consumption was reduced 4-12% in MD and HD pups during the first and second weeks of dosing, compared to controls.

Sexual Development: (males were observed daily from PND 35 until preputial separation, at which time BW was recorded; females were observed daily from PND 28 until vaginal opening occurred, at which time BW was recorded)

Preputial separation was significantly delayed by 1.8 days in HDM and by 1.5 days in MDM compared to controls.

Vaginal opening was significantly delayed by 3.1 days in HDF and by 1.6 days in MDF compared to controls.

Estrous Cycling: (females in the post-treatment subgroup scheduled for mating were examined daily by vaginal smear to determine the stage of estrus starting at least one week after the last day of dosing, and 10 days prior to initiation of cohabitation, and continuing until there was evidence of mating or the 20-day cohabitation period ended)

No treatment-related changes were observed.

Mating: (at ~16 wks of age, 10 F/group were cohabitated with 10 M/group from the same treatment group by transferring each female to the male's cage. Cohabitation continued until positive evidence of mating was detected [i.e., if sperm was observed in the vaginal smear and/or if a vaginal plug was observed in situ] or until 20 nights had elapsed.)

No treatment-related changes were observed in mating performance, fertility, number of corpora lutea, implantations sites, or pre- or post implantation loss.

Neurobehavioral Testing:

Locomotor Activity: (Post-treatment subgroup, 16/sex/group, PND 82-84. Spontaneous activity was measured using an automated Photobeam Activity System during a 60-minute session composed of 12 5-minute intervals. The total number of photobeam breaks occurring during each 5-minute interval was recorded.)

A trend toward increased activity was observed during the first three trials in MDM, HDM, LDF, MDF, and HDF compared to controls.

Open Field Test: (Post-treatment subgroup, 16/sex/group, PND 82-84. Each animal was observed for one minute for abnormalities in posture, gait, behavior, or vocalization.)

No treatment-related changes were observed.

Auditory Startle Habituation Test: (Post-treatment subgroup, 16/sex/group, PND 63-65 and PND 88-94. Each animal was tested in 5 blocks of 10 trials each using a San Diego Instruments' Auditory Startle Response System. Each trial consisted of a burst of white noise at ~120 dB for 50 msec, and was followed by a 10-sec inter-trial interval. Habituation was calculated as the % difference in the response magnitude between trial blocks 1 and 5.)

Percent startle habituation was significantly reduced in HDF compared to control when measured on PND 63-65, but not during the post-treatment period, PND 88-94.

Biel Multiple T Water Maze: (Post-treatment subgroup, 16/sex/group, PND 98-106; each animal was placed in the water maze for a maximum of 3 min per trial, 2 trials per day, with at least 30 min between trials. On Day 1 of the test, the rat had to swim in a straight line to the exit ramp 1.2 meters away. On Days 2-5, the rat had to swim the entire maze, and the number of errors and the time to complete the maze were recorded. Memory was tested on Day 8, after 2 days of rest, by having the rat swim the same maze again.)

No treatment-related changes were observed.

Clinical Pathology: (Blood for hematology [0.25 mL] and clinical chemistry [1.0 mL] studies was collected via puncture of the orbital sinus from rats in the post-treatment subgroup [10/sex/group] on PND 71)

Hematology: (Blood collected into tubes containing EDTA was analyzed for erythrocyte count, hematocrit, hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, leukocyte

count [total and differential], platelet count, reticulocyte count, and erythrocyte and platelet morphology [from smear])

No treatment-related changes were observed.

Clinical Chemistry: (Blood collected into tubes with no anticoagulant was allowed to clot and then centrifuged to obtain serum, which was analyzed for alanine aminotransferase, albumin, albumin/globulin ratio, alkaline phosphatase, aspartate aminotransferase, bilirubin [total and direct], calcium, chloride, creatinine, gamma glutamyl transpeptidase, globulin, glucose, phosphorus, potassium, sodium, total cholesterol, total protein, triglycerides, and urea nitrogen.)

No toxicologically important treatment-related changes were observed.

Toxicokinetics: (Plasma was harvested for TK analysis by centrifugation of blood samples obtained from TK pups [4/sex/time point] on PND 14-15 and from the PND 70 subgroup on PND 67-68 [see Experimental Design section for details]. Plasma samples were flash frozen and stored at -70 °C until analyzed by the Sponsor)

Table 3- Toxicokinetic Parameters of Memantine (Free Base) on Postnatal Days 14 (1 Day after Dose Initiation) and 67 (54 Days after Dose Initiation) following Oral Administration of 15, 30, and 45 mg/kg/day of Memantine in Male and Female Juvenile Rats

Gender	Day	Dose (mg/kg/day)	T_{max} (hr)	C_{max} (ng/mL)	$AUC_{0.5-24}$ (hr*ng/mL)
Male	14	15	4	1165.09	19971
Male	14	30	4	2039.67	27594
Male	14	45	4	3123.6	53930
Male	67	15	1	770.57	6845
Male	67	30	1	1759.47	16294
Male	67	45	0.5	2568.09	21798
Female	14	15	4	1222.78	21906
Female	14	30	4	2279.15	33248
Female	14	45	4	2898.12	52371
Female	67	15	1	1108.38	9888
Female	67	30	1	2323.67	24865
Female	67	45	1	3409.13	46779

(IND 73,075 Volume 118.2, page 407)

Macroscopic Observations: (16/sex/group in the PND 70 subgroups and 16/sex/group in the post-treatment subgroups)

No toxicologically important treatment-related changes were observed.

Organ Weights: (10/sex/group in the PND 70 subgroups and 10/sex/group in the post-treatment subgroups; see Histopathology Table for organs weighed)

No treatment-related changes were observed.

Neurohistopathology: (4/sex/group PND 15, 4/sex/group PND 17, 6/sex/group PND 70, and adult MK-801-treated positive controls [4 M 24-hr postdose; 3 M 72-hr postdose; 3 F 24-hr postdose] were euthanized by i.p. sodium pentobarbital and transcardially perfusion-fixed. The 6/sex/group post-treatment phase brains were not examined since no changes were observed in the PND 70 group, Brains were embedded, freeze-sectioned, and prepared on slides; every 8th section was stained using the de Olmos Amino Cupric Silver method with Neutral red to reveal cell bodies. A subset of 18-20 of the 48-60 slides from each block was examined by (b) (4) All visible brain regions (from PND 15, PND 17, PND 70, and Positive Control groups) were generally examined, but the following areas were specifically examined: the taenia tecta, piriform cortex, and caudal cingulate cortex (retrosplenial cortex). Because of the observation of changes in mammillary bodies, additional intervening sections were stained with amino cupric silver encompassing the rostral to caudal limits of the thalamus. Rating scale: not present = --, barely detectable = 1, light = 2, moderate = 3, heavy/dense = 4)

After oral administration of 0, 15, 30, or 45 mg/kg/day memantine starting on PND 14, the following changes were observed (N=4/sex/group):

Neurodegeneration in the anterior ventral nucleus of the thalamus on PND 15:

Con M:	1	--	--	--	Con F:	1	--	--	--
LDM:	1	--	--	--	LDF:	1	2	2	--
MDM:	1	--	--	--	MDF:	2	--	--	--
HDM:	1	2	3	3	HDF:	1	1	2	--

Neurodegeneration in the anterior ventral nucleus of the thalamus on PND 17:

Con M:	1	--	--	--	Con F:	--	--	--	--
LDM:	2	--	--	--	LDF:	2	--	--	--
MDM:	1	--	--	--	MDF:	2	--	--	--
HDM:	1	2	2	3	HDF:	2	3	3	--

Taken together, the data in the two tables above demonstrate that the incidence and severity of neurodegeneration observed in the anterior ventral nucleus of the thalamus were clearly increased compared to control in HDF and HDM. Slight increases were also observed in LDF and MDF compared to Control F, but too few animals were analyzed to definitively establish that the changes at these doses were treatment-related. Also, repeated dosing for 3 days increased the severity of these lesions in HDF, but not in HDM.

Degenerated cell bodies in the lateral nucleus of the mammillary bodies on PND 15:

Con M:	--	--	--	--	Con F:	--	--	--	--
LDM:	--	--	--	--	LDF:	--	--	--	--
MDM:	1	--	--	--	MDF:	--	--	--	--
HDM:	2	2	2	2	HDF:	1	1	2	--

All animals that had neurodegeneration in the lateral nucleus of the mammillary bodies also had neurodegeneration in the anterior ventral nucleus of the thalamus. No degenerated cell bodies in this region were observed on PND 17, suggesting that the degenerative debris may have been cleared during the intervening two days. These results demonstrate that neurodegeneration in the lateral nucleus of the mammillary bodies was increased compared to control in HDM and HDF. Too few animals were analyzed to definitively establish whether or not the minimal lesions observed in 1/4 MDM on PND 15 were treatment-related.

The data in Table 1 below were not separated out by sex because the Sponsor concluded that “There was no meaningful difference between the sexes for these findings.” (IND 73,075, Volume 118.4, page 1066). The Sponsor also concluded that “There were no meaningful differences between Vehicle Control and the Intermediate and Low dose groups in the PND 15 and 17 animals.” (IND 73,075, Volume 118.4, page 1066). Therefore, the Sponsor considers the NOEL for memantine-induced neurodegeneration in brain to be the MD of 30 mg/kg.

This reviewer considers the NOEL for neurodegeneration in the anterior ventral thalamus to be 30 mg/kg/day for M rat pups, but undetermined for F (≤ 30 mg/kg/day, due to the equivocal increases in incidence and/or severity in F at 15 and 30 mg/kg/day). The NOEL for neurodegeneration in the mammillary bodies is 30 mg/kg/day for F, but is unclear for M rat pups (≤ 30 mg/kg/day, based on equivocal minimal lesions in 1/4 M at 30 mg/kg on PND15 compared to 0/4 in Control M.

Table 1. Incidence of degenerative profiles in Control and Memantine treated animals PND 15 and PND 17

Group	PND 15				PND 17			
	1	2	3	4	1	2	3	4
mg/kg Memantine	**0**	**15**	**30**	**45**	**0**	**15**	**30**	**45**
Number of animals examined (4 males + 4 females per group)	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**
Anterior-ventral thalamus								
Minimal (barely detectable)	2	2	1	3	1	0	1	1
Slight (light)	0	2	1	2	0	2	1	3
Moderate	0	0	0	2	0	0	0	3
Total	2	4	2	7	1	2	2	7
Mammillary bodies:								
Minimal (barely detectable)	0	0	1	2	0	0	0	0
Slight (light)	0	0	0	5	0	0	0	0
Total	0	0	1	7	0	0	0	0

(IND 73,075 Volume 118.4, page 1066)

No treatment-related changes were observed in brains from the PND 70 or Post-treatment subgroups.

Eight adult males given 10 mg/kg i.p. MK-801 showed recumbency, decreased activity, flushed extremities, and clonic movements, but 7 recovered after ~24 hrs; one was found dead. Eight adult females given 5 mg/kg i.p. MK-801 showed prostration, lethargy, shallow breathing, flushed extremities, and clonic movements. Four F partially recovered by 24 hrs postdose, but four remained extremely ataxic and unable to eat or drink, so they were euthanized for humane reasons. Four M and 3 F rats were killed and perfusion-fixed on PND 15, and 3 M were killed and perfusion-fixed on PND 17. Brains were processed for detection of neurodegeneration. Both M and F showed degenerated neuron cell bodies, dendrites, and axons in the caudal cingulate cortex, as expected. Neither individual nor summary data were provided regarding the incidence and severity of neurodegeneration observed in positive control animals.

Microscopic Observations: (Tissues listed in the Histopathology Table below from 10/sex/group in the PND 70 subgroups and 10/sex/group in the post-treatment subgroups were preserved in 10% neutral buffered formalin [testes and eyes were initially immersed in Modified Davidson's solution]; only tissues from Control and High Dose groups from the PND 70 subgroup were examined microscopically. Standard procedures were used.)

Adequate Battery: Yes, only the following tissues were missing from the standard list: fallopian tubes, harderian gland, larynx, cervical lymph node, nasal cavity, sciatic nerve, and pharynx.

Peer Review: No.

Histological Findings: No treatment-related changes were observed, except non-adverse minimal increases in the level of extramedullary hematopoiesis in spleen (4/10 HDM, 2/10 HDF).

Conclusions:

Treatment of M and F PND14 rat pups with Memantine HCl for 1-3 days at 15, 30, or 45 mg/kg/day via oral gavage resulted in treatment-related minimal to moderate neurodegeneration in the anterior ventral thalamus and/or the lateral nucleus of the mammillary bodies at the HD of 45 mg/kg/day. The minimal to mild neurodegeneration in these brain areas appeared to be slightly increased in incidence and/or severity in the MD and LD groups compared to controls, but, because of the low number of animals included in this study, it was not possible to determine whether or not these differences were treatment-related.

Treatment of M and F rat pups with Memantine HCl at 15, 30, or 45 mg/kg/day via oral gavage from PND14 to PND70 resulted in slight reductions in final body weight and food consumption during the first two weeks, delayed preputial separation and vaginal opening, slightly increased locomotor activity, reduced habituation to auditory startle, and minimal increases in the level of extramedullary hematopoiesis in spleen. No neurodegeneration was observed in brain sections, using amino cupric silver stain. None of the changes observed in this phase of the study seem to be particularly adverse, based on their small magnitude and/or their transient nature. The delays in reaching sexual maturity did not affect reproductive capabilities. However, the neurodegeneration described above in pups sacrificed after only 1-3 days of treatment at ≥ 15 mg/kg/day is of concern.

Histopathology Table

Tissue	Weighed	Preserved (All groups)	Microscopic Examination (Control and High Dose)
adrenals	X	X	X
aorta (thoracic)		X	X
bone marrow smear (rib)[a]		X	[b]
bone (sternum, femur with joint)		X	X
bone marrow (sternum, femur)		X	X
brain (medulla, pons, cerebrum and cerebellum)	X	X	X
epididymides		X	X
esophagus		X	X
eyes (with optic nerve)		X	X
heart	X	X	X
kidneys	X	X	X
lacrimal glands		X	X
large intestine (cecum, colon and rectum)		X	X
liver		X	X
lungs (with mainstem bronchi)		X	X
lymph node (mesenteric, mediastinal)		X	X
mammary gland or mammary region		X	X
mesentery		X	X
muscle (*biceps femoris*)		X	X
nerve (sciatic)		X	X
ovaries	X	X	X
pancreas		X	X
Peyer's patches		X	X
pituitary	X	X	X
prostate	X	X	X
salivary glands (submandibular)		X	X
seminal vesicles	X	X	X
skin		X	X
small intestine (duodenum, ileum and jejunum)		X	X
spinal cord (cervical, thoracic, lumbar)		X	X
spleen	X	X	X
stomach		X	X
testes		X	X
thymus	X	X	X
thyroid (with parathyroid)	X	X	X
trachea		X	X
urinary bladder		X	X
uterus (horns/body/cervix)	X	X	X
vagina		X	X
gross lesions		X	X
target organs		X	X

[a]Qualitative examination of bone marrow sections were performed. Bone marrow smears were prepared from the rib.

(IND 73,075 Volume 4.4, pages 42-43)

11 Integrated Summary and Safety Evaluation

Two juvenile animal toxicity studies submitted to IND 73,075 (for the treatment of autism in children, currently active in the Division of Psychiatry Products) have been reviewed here because they are relevant to the Sponsor's proposed addition to the Animal Toxicology section of the Package Insert describing the results of the definitive study.

In the preliminary juvenile toxicity study (MEMTX22000), administration of memantine HCl to male and female Sprague-Dawley rat pups via oral gavage at 5 mL/kg in distilled water once daily from PND 14 to PND 35 was well tolerated at 15 and 30 mg/kg/day, but dosing at 60 and 120 mg/kg/day was stopped on Day 4 due to clinical signs (decreased activity, prostration, labored breathing, and/or piloerection) and/or excessive body weight loss (15-30%).

In the definitive juvenile toxicity study (MEMTX23000), administration of memantine HCl to male and female Sprague-Dawley rat pups via oral gavage at 5 mL/kg in distilled water once daily from PND 14 to PND 70 resulted in the following minor changes at 30 and/or 45 mg/kg/day: slight reductions in final body weight, delayed preputial separation and vaginal opening, slightly increased locomotor activity, reduced habituation to auditory startle, and minimal increases in the level of extramedullary hematopoiesis in spleen. No neurodegeneration was observed in brain sections, using amino cupric silver stain. None of the changes observed in this phase of the study seem to be particularly adverse, based on their small magnitude and/or their transient nature. The delays in reaching sexual maturity did not affect reproductive capabilities.

However, treatment-related neurodegeneration was observed in rat pups sacrificed 24 hours following treatment for 1-3 days (PND14-16) with memantine HCl at 15, 30, and 45 mg/kg/day. Minimal to moderate neurodegeneration in the ventral anterior nucleus of the thalamus was observed in 4/4 HDM and 3/4 HDF on PND15 and in 4/4 HDM and 3/4 HDF on PND17. Minimal to mild neurodegeneration in the lateral nucleus of the mammillary bodies was observed in 4/4 HDM and 3/4 HDF only on PND15. The Sponsor agrees that these changes observed in HDM and HDF pups were treatment-related, but contends that the minimal to mild changes observed in the ventral anterior nucleus of the thalamus of the MD (1/4 M, 1/4 F [mild] on PND15; 1/4 M, 1/4 F [mild] on PND17) and LD (1/4 M, 3/4 F [2 mild] on PND15; 1/4 M [mild], 1/4 F [mild] on PND17) groups were not meaningfully different from the minimal neurodegeneration observed in the vehicle control groups (1/4 M, 1/4 F on PND15; 1/4 M, 0/4 F on PND17). The Sponsor also dismissed the relevance of the minimal neurodegeneration observed in the lateral nucleus of the mammillary bodies in 1/4 MDM on PND15 even though no changes were observed in any M or F controls.

Therefore, the Sponsor considers the NOEL for neurodegeneration in rat pups to be 30 mg/kg/day for both M and F (associated Cmax = 2040 ng/mL [M], 2279 ng/mL [F]; $AUC_{0\text{-}24\ hr}$ = 27594 ng*hr/mL [M], 33248 ng*hr/mL [F]).

This reviewer, however, considers the NOEL for neurodegeneration to be uncertain. The greater incidence and severity of neurodegeneration observed in the thalamus in the LDF group compared to controls suggests that these lesions may be treatment-related, but the MDF group showed no increase in incidence and only a slight increase in severity. The observation of minimal neurodegeneration in the mammillary bodies in 1/4 MDM brains on PND 15 was increased over the 0/4 observed in controls, but this is a very small difference that may be due to the small number of brains analyzed. Overall, the number of animals included in this study was insufficient to definitively assess whether or not the changes in the LD and MD groups were treatment-related. The lesions observed in the HD groups clearly appeared to be treatment-related.

If memantine is to be developed for a pediatric indication, then consideration should be given to requiring a new study to clearly establish the NOEL for neurodegeneration in male and female rat pups. The new study should include an expanded histopathology of the brain, with a thorough analysis of the rostral to caudal extent of the thalamus and the mamillary bodies, with at least 20 pups/sex/group given single doses of memantine HCl on PND14 for neurohistopathology, and appropriate numbers of animals in satellite toxicokinetic groups.

The Animal Toxicology section of the label should also include a description of the results of a 28-day oral combination neurotoxicity study of memantine HCl and donepezil HCl in female rats (Study MEM-TX-27) submitted to IND 33,392 (Serial #612, submitted 12 FEB 2009; reviewed in detail elsewhere). The results of this study supported the conclusions of Creeley et al. (*Neurobiology of Aging 29:153-167, 2008*) that coadministration of donepezil with memantine can lower the threshold for, increase the severity of, and extend the range of brain areas affected by the neurodegeneration induced by memantine in female rats. While the incidence of neurodegeneration within each group was lower in this oral study than the 6/6 rats reported by Creeley et al. (2008) with i.p. administration of 30 mg/kg MEM + 10 mg/kg DPZ, marked treatment-related lesions were observed in 1/9 rats at 30/10 mg/kg/day p.o., but no lesions were observed at 30/3 or 30/0; and moderate to marked lesions were observed in 1/7 rats at 60/10 p.o. in several brain areas not affected in groups treated with 60/3, 60/0, or MK-801, the positive control (olfactory nucleus, temporal cortex, perirhinal cortex, frontal cortex, and insular cortex). Lesions observed at 60/3 and 60/0 were limited to mild neurodegeneration in the retrosplenial cortex (in 1/9 rats, and 1/10 rats, respectively). Positive control rats showed mild to marked lesions in the areas expected for an NMDA receptor antagonist (retrosplenial cortex, piriform cortex, entorhinal cortex, amygdaloid nucleus and/or a few other areas). In a letter of 20 MAY 2010, the Sponsor was asked to further characterize the effects of the combination of memantine and donepezil by conducting a single dose oral neurotoxicity study in adult female rats with memantine in the presence and absence of donepezil at a maximum tolerated dose.

The NOEL for neurodegeneration of 10 mg/kg/day MEM + 10 mg/kg/day DPZ was associated with MEM Cmax = 324 ng/mL (D1), 428 ng/mL (D28), $AUC_{0\text{-}24\ hr}$ = 2821 ng*hr/mL (D1), 3449 ng*hr/mL (D28); and DPZ Cmax = 265 ng/mL (D1), 467 ng/mL (D28), $AUC_{0\text{-}24\ hr}$ = 2348 ng*hr/mL (D1), 3035 ng*hr/mL (D28); and DPZ Cmax = 265

ng/mL (D1), 467 ng/mL (D28), $AUC_{0\text{-}24\ hr}$ = 2348 ng*hr/mL (D1), 3035 ng*hr/mL (D28). (Note: estimated mean steady state DPZ plasma exposures in humans at 10 mg/day DPZ are Cmax = 60 ng/mL and $AUC_{0\text{-}24\ hr}$ = 1138 ng*hr/mL [see Tiseo et al, 1998]; the mean plasma exposures in rat at 10 mg/kg/day DPZ shown above exceed these estimated human exposures by 4.4-7.8X for Cmax, and 2.1-2.7X for $AUC_{0\text{-}24\ hr}$.)

Table 1 below summarizes the estimated safety margins based on MEM plasma exposures (Cmax and $AUC_{0\text{-}24\ hr}$) in juvenile and adult rats at the no-effect levels for neurodegeneration compared to expected mean steady state plasma exposures of MEM at the maximum recommended clinical dose of 28 mg/day Namenda® XR.

Table 1

Estimated Safety Margins Based on Expected Memantine Plasma Exposures in Humans at the Maximum Recommended Dose of 28 mg/day Namenda ® XR

Toxicity	Species	NOEL	Safety Margin Based on AUC*	Safety Margin Based on Cmax#
Neuro-degeneration in the anterior ventral thalamus	M Rat Pup PND14-16	30 mg/kg/day	9.0	13
	F Rat Pup PND14-16	≤ 30 mg/kg/day@	≤ 11	≤ 14
Neuro-degeneration in the lateral nucleus of the mamillary bodies	M Rat Pup PND14-16	≤ 30 mg/kg/day$	≤ 9.0	≤ 13
	F Rat Pup PND14-16	30 mg/kg/day	11	14
Marked neuro-degeneration in the entorhinal cortex	Adult F Rat	10 mg/kg/day (for 28 days, in the presence of 10 mg/kg/day donepezil)	0.9 (Day 1) 1.1 (Day 28)	2.0 (Day 1) 2.6 (Day 28)

*Steady state memantine $AUC_{0\text{-}24\ hr}$ in human: 3058 ng•hr/ml at 28 mg/day Namenda® XR.
#Steady state memantine Cmax in human: 163 ng/mL at 28 mg/day Namenda® XR.
@Treatment-related lesions were observed in at 45 mg/kg/day, but it was not clear if lesions observed in F at 15 or 30 mg/kg/day were related to treatment.
$Treatment-related lesions were observed at 45 mg/kg/day, but it was not clear if lesions observed in M at 30 mg/kg/day were related to treatment.

This application is approvable.

The results in juvenile animals suggest that further work may be needed to support a pediatric indication for memantine. The lack of an adequate safety margin between expected clinical plasma exposures and those at the NOEL for neurodegeneration in adult rats given memantine in the presence of donepezil also presents cause for concern, and has prompted a request to the Sponsor to further characterize this toxicity

in single dose studies. However, given that the relevance to humans of this toxicity in rodent brain remains unknown, the risks to patients with moderate to severe Alzheimer's disease concurrently taking a cholinesterase inhibitor must be weighed against the potential clinical benefits.

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22525	ORIG-1	FOREST LABORATORIES INC	NAMENDA XR(MEMANTINE HCL)ER CAPSULES

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/s/

DAVID B HAWVER
06/13/2010

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06/15/2010